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Sensations and regional brain responses evoked by tussive stimulation of the airways☆

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ABSTRACT

Stimuli that evoke cough in humans also elicit a sensation described as the urge-to-cough. This sensation is perceived at levels of stimulation below the threshold for coughing and increases in intensity in response to higher levels of stimulation. Cough in humans can be consciously modified in intensity or suppressed altogether, and the urge-to-cough is likely to contribute to discretionary responses to tussive stimulation. Converging evidence from animal and human experiments have identified a widely distributed network of brain regions that are implicated in the representation of urge-to-cough and the control of coughing. This network incorporates regions that show responses associated with urge-to-cough ratings, such as limbic and somatosensory cortices, as well as paralimbic and premotor regions implicated in response inhibition that activate in association with efforts to suppress cough. The urge-to-cough can be influenced by psychological factors and preliminary findings suggest that these effects could be mediated by top-down influences. There is considerable impetus to understand circuits involved in the modulation of urge-to-cough because it may be possible to antagonise the troubling sensation while preserving the critical cough reflex.

1. Introduction

Cough is a motor response that expels particulate matter from the airways, thus contributing to the preservation of airway patency and hence the maintenance of respiratory function. Although cough can be enlisted voluntarily, the typical mode of induction of defensive coughing is reflexively following stimulation of the airways through a pathway involving vagal afferents and processing at the level of the brainstem. This short loop pathway ensures a rapid response to airway irritation that reduces the risk of aspirated substances reaching the airways and lungs as well as aiding with efficient clearance of intrinsically generated material such as secretions. In addition to the motor behaviour, stimuli likely to evoke cough also give rise to a sensory experience, commonly referred to as the urge-to-cough (Davenport et al., 2002). Interest in the character and mechanisms of urge-to-cough is growing as clinicians and researchers recognise that the sensation can be a troublesome symptom of airways disease in its own right, that clinical cough could in part be a discretionary behaviour motivated by a drive to satiate the urge-to-cough, and that antagonism of the urge-to-cough could be a viable treatment strategy that would leave the critical cough reflex intact (Chung, 2011; Mazzone et al., 2011b; Morice, 2013; Morice et al., 2012). This review will discuss recent advances in the understanding of urge-to-cough that have been facilitated by heightened interest in the sensation.

1.1. Sensory attributes of the urge-to-cough

The urge-to-cough is a latent process. Psychophysical investigations of the sensation have been confined to experiments involving humans, in whom language provides a means to convey personal experience. Studies of endogenously derived urge-to-cough (for example, in airways disease) are limited and have only reported measures of severity rather than investigating mechanistic processes. For this reason we will limit our discussion to experimentally induced urge-to-cough, which typically involves the inhalation of nebulised solutions containing varied doses of tussive substances such as capsaicin (Davenport et al., 2002) and citric acid (Yamanda et al., 2008), or the use of other stimuli such as inhalation of distilled water (fog) (Lavorini et al., 2007) or application of puffs of air (Hegland et al., 2011). The quality of the sensation evoked by tussive stimuli is not well characterised but has been described as itching, scratching or burning, and is usually localised

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to the pharynx and/or larynx. Additionally, the sensation is associated with a desire to cough. There has been speculation that the urge-to-cough is also likely to be invested with a negative emotional valence, or unpleasantness, but evaluations of this attribute have not been reported to date (Farrell et al., 2012). Unlike in disease where the endogenous urge-to-cough can be persistent and difficult to satiate, the duration of experimentally-induced urge-to-cough is relatively short-lived. A single inhalation of a tussive substance will usually give rise to an urge-to-cough during the inhalation and subsequent exhalation, and no longer be noticeable upon the initiation of the next inhalation of fresh air (Farrell et al., 2012). The temporal pattern of urge-to-cough during inhalation of a tussive substance is distinct from other sensations that can feasibly arise in association with stimulation. Whereas urge-to-cough is closely related to the respiratory cycle, other sensations associated with capsaicin inhalation, such as heat in the mouth, taste, watering of the eyes, etc. usually only occur after repeated doses and persist for minutes with no appreciable variability relative to the respiratory cycle (Mazzone et al., 2007).

The intensity of urge-to-cough varies according to the intensity of stimulation. Stimulus–response functions for urge-to-cough are typically derived using doubling doses of tussive substances. The lowest dose required to elicit a detectable urge-to-cough has been dubbed the urge-to-cough threshold, or Cu (Dicpinigaitis et al., 2011). The relatively recent appearance in the literature of Cu measures reflects the growing interest in the sensation, and complements the traditional motor-related thresholds such as the C2 and C5, which are the lowest doses of a tussive stimulus that elicit two or five coughs (Choudry and Fuller, 1992). Single breaths of doubling doses of tussive stimuli in excess of the Cu generally evoke monotonic increases in the urge-to-cough in healthy people (Davenport et al., 2002). The stimulus–response function has a decelerating profile when plotted against real stimulus values, and research groups tend to present psychophysical outcomes using logarithmic dose values that display a linear relationship with urge-to-cough ratings.

Personal attributes and behaviours systematically influence the slope, but not the intersect of the urge-to-cough stimulus–response function. For instance, the slope of the response function is steeper in women than men, but the Cu does not differ between the sexes (Dicpinigaitis et al., 2012; Gui et al., 2010). The Cu is also comparable among smokers and non-smokers, although smoking is associated with a decrease in the slope of the urge-to-cough stimulus–response function (Kanezaki et al., 2012, 2010), which trends towards normal levels when smoking is ceased (Dicpinigaitis et al., 2006). Advancing age is associated with a decrease in the intensity of urge-to-cough at motor thresholds (i.e. C2, C5), which do not show age-related changes, whereas interpolated values of the Cu are stable across groups of disparate age (Ebihara et al., 2011). The general conclusion from these assessments of urge-to-cough is that the level of stimulation requisite for the detection of any urge-to-cough is relatively stable, but that both increased and decreased sensitivity to supra-threshold stimuli can be observed in healthy cohorts depending on age, sex and exposure to cigarette smoke.

The urge-to-cough is subject to considerable within-subject variance during repeated presentations of stimuli. Adaptation to tussive stimulation has been observed in experiments involving multiple inhalations of fixed intensity doses (Choudry et al., 1989; Farrell et al., 2012; Mazzone et al., 2007). Indeed, in some individuals a dose initially eliciting a moderate level of urge-to-cough can fail to evoke any appreciable sensation after repeated inhalations during tens of minutes (Mazzone et al., 2007). Psychological factors have demonstrable effects on the urge-to-cough within the same person. An increase in ratings of urge-to-cough occurs when anxiety increases (Davenport et al., 2009) and when attention shifts from an exteroceptive to an interoceptive focus (Janssens et al., 2014), whereas administration of a placebo erroneously ascribed with antitussive benefits can dramatically decrease ratings of urge-to-cough under experimental conditions (Leech et al., 2012). Non-systematic variance is also a feature of urge-to-cough responses among participants inhaling capsaicin. Very large coefficients of variation (56–75%) have been reported for intermittent breaths of capsaicin at fixed doses (Farrell et al., 2012), as well as for repeated estimates of urge-to-cough during continuous inhalation of a single dose for several minutes (Farrell et al., 2014). Visceroafferent sensations are generally less reliably described during magnitude estimation procedures compared to sensations arising from cutaneous stimuli, and this inconsistency could be related to differences in the central representation of the viscera in sensory processing regions of the brain (Strigo et al., 2002). However, despite considerable variability within participants, averaging over repeated trials consistently identifies intensity-dependence of urge-to-cough responses to tussive stimuli.

1.2. Urge-to-cough and the likelihood of coughing

Perception of an urge-to-cough occurs at levels of stimulation that are typically less than the threshold for coughing (Davenport et al., 2002) (Fig. 1A). It is difficult to provide estimates of the difference between the Cu and cough-motor thresholds by amalgamating outcomes across studies because lack of consistent methods has a bearing on results (Ternesten-Hasseus et al., 2006), but a report from one study of differential scores calculated on a case-by-case basis estimated that the urge-to-cough is elicited at approximately two doses increments lower than the threshold for one or more coughs (Dicpinigaitis et al., 2012). The presence of an urge-to-cough at stimulus levels that do not evoke a cough has important implications for the role of cognitive processes in the control of coughing. Sensitivity to low levels of airways irritation captures attention and provide opportunities to engage in discretionary behaviour (Davenport, 2008). Many aspects of coughing are under conscious control in humans, and an awareness of airways irritation has the potential to interact with motor planning. For instance, coughing can be suppressed or modelled (i.e. actively increased or decreased in intensity or duration) in response to stimuli that evoke an urge-to-cough (Hegland et al., 2012; Hutchings et al., 1993). Indeed, coughing can be initiated voluntarily in the absence of any interoceptive trigger.

Voluntary control of coughing impacts on the relationship between intensity of urge-to-cough and the likelihood of coughing. The most readily apparent influence of voluntary control on the association between urge-to-cough and coughing is conscious suppression. In the absence of any motivation to suppress coughing, the delivery of a tussive dose that evokes two coughs (C2) is likely to be associated with a low to moderate level of urge-to-cough (Farrell et al., 2012). However, the simple instruction to participants to suppress coughing can profoundly increase the dose required to evoke an uncontrolled response, despite the reported experience of increasing levels of urge-to-cough (Hutchings et al., 1993). Consequently, this “dynamic motor threshold” (Hegland et al., 2011) means that reported levels of urge-to-cough have limited utility as a predictor of the likelihood of coughing. It may be that participants’ judgements of urge-to-cough under conditions of conscious suppression are representative of the level of effort required to avert coughing, although this proposition is yet to be tested.

1.3. Neural structures implicated in the urge-to-cough

1.3.1. Peripheral receptors and fibres

The cell bodies of afferents implicated in cough are located in the nodose and jugular ganglia of the vagal nerves (Canning et al., 2004).